REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is respectfully requested. As set forth above, Applicant has canceled claims 13, 14, 18, 20, 22, 24-26, 28, 29, 33, 35, 39, 41, 43 and 45-48 without prejudice to the filing of any divisional, continuation, or continuation-in-part application, which is to merely expedite allowance of the subject application. Applicant hereby submits new claims 54-58. Applicant further submits that claims 12, 15-17, 19, 21, 23, 27, 30, 32, 36-38, 40, 42 and 44 have been amended to more clearly define the subject matter encompassed by the Applicant's invention. Support for the new claims and claim amendments may be found in the specification, in part, at Example 1, at Example 4, and at Figure 7 (*see, e.g.*, claims 12, 16, 27, 37, and 54); at page 8, line 4 and at Example 1 (*see, e.g.*, claims 17, 19, 21, 38, 40, 42, and 55-57); and at Examples 4-5 and 7 (*see, e.g.*, claims 58). No new matter has been added. Therefore, claims 12, 15-17, 19, 21, 23, 27, 30, 32, 36-38, 40, 42, 44, and 54-58 are currently pending.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The first of the attached pages is captioned "Version With Markings to Show Changes Made."

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

(1) In the Office Action dated August 15, 2001, claims 16, 18, 20, 22, 24, 26, 37, 39, 41, 43, 45 and 47 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. In particular, it is alleged that the claimed recombinant fusion polypeptide comprising an immunogenic portion that comprises "six" immunogenic peptides from the same serotype is not supported in the specification and, therefore, these claims are considered to encompass new matter.

Applicant respectfully traverses this ground of rejection and submits that the claims directed to a recombinant fusion polypeptide having an immunogenic portion with six immunogenic peptides is adequately described in the instant specification, which would convey to a person having ordinary skill in the art that Applicant had possession of the claimed invention at the time the subject application was filed. As disclosed in the specification (*see, e.g.*, page 2,

lines 6-18) and recited in the claims, the instant invention is directed, in pertinent part, to a fusion polypeptide comprising a multivalent immunogenic portion and a C-terminal peptide that protects the immunogenicity of the immunogenic portion, wherein the immunogenic portion consists of six immunogenic peptides and *at least one* of the immunogenic peptides is from a Group A Streptococci serotype of 1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 or 56. Hence, contrary to the assertion in the Office Action, Applicant respectfully submits that the claims are not so limited as to encompass fusion polypeptides having an immunogenic portion comprising six immunogenic peptides of "only" the same serotype. As recited in claim 15, all that is required is *at least one* immunogenic peptide from one of the recited serotypes, although all six may be the same. Furthermore, Applicant has taught how to make and use a fusion polypeptide according to the instant invention (*see, e.g.*, fusion polypeptide M24-M6-M5-M19-M1-M3-M24 of Figure 1 and as described at Examples 1 and 4), which is a preferred embodiment that has at least one Group A Streptococci serotype recited in the claims. Moreover, Applicant respectfully submits that it is well-established that an Applicant need not disclose every species encompassed by a claim (*see, e.g.*, *In re Angstadt* 190 USPQ 214, CCPA 1976) and that the mere lack of a verbatim description in the specification is not sufficient to carry the initial burden of establishing lack of written description (*see, e.g.*, *In re Edwards* 196 USPQ 465, CCPA 1977).

Accordingly, Applicant respectfully submits that the instant specification adequately describes the subject matter encompassed by the claims so as to reasonably convey to a person having ordinary skill in the art that Applicant, at the time of filing the instant application, had possession of the claimed invention. Thus, Applicant requests that this rejection be withdrawn because the requirements under 35 U.S.C. §112, first paragraph have been satisfied.

(2) In the Office Action, claims 13 and 28 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. More specifically, it is alleged that the claimed reiterated C-terminal "peptide" comprising an immunogenic peptide is not supported in the specification because there is only disclosure of a "reiterated immunogenic polypeptide" and, therefore, these claim are considered to encompass new matter.

Applicant respectfully traverses this ground of rejection and submits that the claims directed to fusion polypeptide having a C-terminal peptide that is a reiteration of at least one immunogenic "peptide" is adequately described in the instant specification, which would convey to a person having ordinary skill in the art that Applicant had possession of the claimed invention at the time the subject application was filed. Applicant respectfully submits that the terms "immunogenic peptide" and "immunogenic polypeptide" are used interchangeably in the instant specification. For example, a person having ordinary skill in the art would understand that an "immunogenic polypeptide" of certain preferred embodiments, such as a fragment from the first 50 amino acids of the M protein amino-terminus (*see, e.g.*, specification at page 5, lines 25-26), are also an "immunogenic peptide." Furthermore, the instant specification teaches how to identify M protein "peptides" suitable for use as an "immunogenic polypeptide" according to the instant invention (*see, e.g.*, specification at page 6, line 4 through page 7, line 28), and explicitly teaches a reiterated "immunogenic peptide" in Example 4 (*see, e.g.*, specification at page 20, line 28 through page 21, line 2).

Accordingly, Applicant respectfully submits that the instant specification adequately describes the subject matter encompassed by the claims so as to reasonably convey to a person having ordinary skill in the art that Applicant, at the time of filing the instant application, had possession of the claimed invention. Thus, Applicant requests that this rejection be withdrawn because the requirements under 35 U.S.C. §112, first paragraph have been satisfied.

REJECTION UNDER 35 U.S.C. §102(b)

In the Office Action, claims 12-15, 17, 19, 21, 23, 25, 27-31, 36, 38, 40, 42, 44 and 46 were rejected under 35 U.S.C. §102(b) as anticipated by WO 94/06421 (Dale and Lederer). In particular, it is alleged that Dale and Lederer disclose a recombinant fusion or hybrid polypeptide, and a composition for promoting an immune response with such a fusion polypeptide, according to the instant invention.

Applicant respectfully traverses these grounds of rejection and submits that Dale and Lederer fail to meet every limitation of the instant claims and, therefore, fail to anticipate the claimed invention. As described in the specification (*see, e.g.*, page 2, lines 6-18) and recited in

the amended claims, the instant invention is directed, in pertinent part, to a recombinant fusion polypeptide comprising (a) a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci and (b) a C-terminal peptide that protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci. As discussed in greater detail below, Applicant respectfully submits that Dale and Lederer fail to disclose a C-terminal peptide that is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion, that protects the immunogenicity of the immunogenic portion, and that is not required to stimulate an immune response against Group A Streptococci.

Dale and Lederer provide a multivalent hybrid M protein consisting of *different* M protein peptides, which are all "immunogenic peptides" (*see, e.g.*, Dale and Lederer, Figures 1, 5, and 13, respectively). Therefore, Dale and Lederer, while teaching an immunogenic hybrid protein consisting of "immunogenic peptides," fail to teach or suggest a recombinant fusion polypeptide having an immunogenic portion comprising immunogenic peptides *and* a C-terminal peptide that is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion, that protects the immunogenicity of the immunogenic portion, and that is not required to stimulate an immune response against Group A Streptococci. Moreover, Applicant respectfully submits that the hybrid proteins of Dale and Lederer *lack* a protective C-terminal peptide (*i.e.*, a reiterated immunogenic peptide) because the Dale and Lederer hybrid M proteins failed to elicit a strong antibody response to the carboxy-terminal "immunogenic peptide" (*see, e.g.*, Dale and Lederer at page 30, third full paragraph).

Furthermore, Applicant respectfully submits that Dale and Lederer fail to teach or suggest a recombinant fusion polypeptide comprising a multivalent immunogenic portion of immunogenic peptides and C-terminal peptide that is a reiteration of at least one immunogenic peptide from the *amino-terminal* of the immunogenic portion. As noted in the Office Action, Dale and Lederer disclose a multivalent hybrid protein with repeated (*i.e.*, reiterated) "immunogenic peptides" ($[M24]_3$-$[M5]_3$-$[M6]_3$-$[M19]_3$); however, the reiterated C-terminal

peptide (M19) is not a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion (M24 or M5). In addition, Dale and Lederer used the repeated subunits within the hybrid M protein to help evoke antibodies to the distal (*i.e.*, carboxy-terminal) epitopes (*see* Dale and Lederer, at page 27, lines 17-20) and, therefore, fail to teach or suggest a protective C-terminal peptide, much less a C-terminal peptide that is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion. Therefore, Applicant submits that Dale and Lederer fail to provide every element of the instant claims.

Accordingly, Applicant respectfully submits that the instant claims distinguish patentably over Dale and Lederer and, therefore, satisfy the requirements of 35 U.S.C. §102(b). Applicant requests that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. §103(a)

In the Office Action, claims 27 and 32-35 were rejected under 35 U.S.C. §103(a) as obvious over WO 94/06421 (Dale and Lederer) in view of U.S. Patent No. 5,334,379 (Pillai *et al.*). More specifically, it is asserted that it would have been obvious for a person having ordinary skill in the art, at the time the instant invention was made, to add the IL-2 or IL-4 of Pillai *et al.* to the hybrid M protein of Dale and Lederer, to arrive at the composition of the claimed invention with a reasonable expectation of success.

Applicant respectfully traverses this ground of rejection and submits that Dale and Ledeerer and Pillai *et al.*, taken alone or in combination, fail to teach or suggest the claimed invention and, further, would not have motivated a person having ordinary skill in the art to arrive at the claimed invention with a reasonable expectation of success. The present invention is directed, in pertinent part for this rejection, to a composition for promoting an immune response against Group A Streptococci, comprising a pharmaceutically acceptable carrier and a recombinant fusion polypeptide comprising (a) a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci and (b) a C-terminal peptide that protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion and is not required to stimulate an immune response

against Group A Streptococci. As set forth above, Dale and Lederer fail to teach or suggest a recombinant fusion polypeptide with an immunogenic portion and a C-terminal peptide that is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion, that protects the immunogenicity of the immunogenic portion, and that is not required to stimulate an immune response against Group A Streptococci. Furthermore, as set forth in the Office Action, Dale and Lederer concededly fail to teach or suggest a recombinant fusion polypeptide composition further comprising an immunomodulatory cofactor.

Applicant respectfully submits that the disclosure of Pillai *et al.* fails to remedy the deficiencies of Dale and Lederer and, therefore, the combination of Pillai *et al.* with Dale and Lederer fails to teach or suggest the instant invention. Pillai *et al.* merely disclose the use of immunogenic conjugates of carbohydrate-containing antigen conjugated with immunomodulatory factors to enhance the immunogenicity of the antigen. More specifically, Pillai *et al.* provide a method for enhancing the immunogenicity of the poorly immunogenic bacterial capsular polymers and for increasing the half-life of immunomodulatory factors *in vivo*. However, Pillai *et al.*, while teaching the use of immunomodulatory factors, fail to teach or suggest any type of recombinant fusion polypeptide, much less a recombinant fusion polypeptide comprising a multivalent immunogenic portion and a C-terminal peptide that protects the immunogenicity of the immunogenic portion. In addition, Pillai *et al.* actually teach away from the use of immunomodulatory factors in a mere admixture, although the instant claims are not so limited, because these factors show toxic effects and have short half-lives (*see* Pillai *et al.* at column 1, lines 26-30). In fact, Pillai *et al.* are silent with regard to a composition for promoting an immune response against Group A Streptococci and, consequently, fail to provide a suggestion or motivation to a person having ordinary skill in the art to combine Pillai *et al.* with Dale and Lederer. Applicant respectfully submits that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination *prima facie* obvious, as the prior art must also suggest the desirability of the combination (*see, e.g.*, *In re Mills*, 16 USPQ2d 1430, Fed. Cir., 1990; *In re Fritch*, 23 USPQ2d 1780, Fed. Cir., 1992).

Hence, Applicant respectfully submits that the Office Action has not set forth a *prima facie* case of obviousness, where the cited references fail to teach every limitation of the instant invention and fail to provide motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success. Accordingly, Applicant respectfully submits that the instant claims distinguish patentably over Dale and Lederer and Pillai *et al.*, therefore, satisfy the requirements of 35 U.S.C. § 103(a). Applicant requests that this rejection be withdrawn.

OBJECTIONS

In the Office Action, claims 1 and 31 were objected to for grammatical errors. However, claim 1 is not currently pending and the claim terms referred to are not present in the instant claims. It is unclear whether these objections are directed to the subject application or a different application. Applicant requests clarification.

All of the claims pending in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,

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Applicant : James B. Dale
Application No. : 09/151,409
Attorney Docket No. : 481112.410

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 2, line 6, has been amended as follows:

Briefly stated, the present invention provides immunogenic synthetic fusion polypeptides which stimulate an immune response against Group A streptococci. Within one aspect such polypeptides comprise (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating an immune response against Group A streptococci, and a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion. Within preferred embodiments, the C-terminal peptide is not required to stimulate an immune response against Group A streptococci and hence, may be an inconsequential non-immunogenic peptide, or a reiterated immunogenic polypeptide. Within certain embodiments, the immunogenic polypeptide can be obtained from a wide variety of Group A streptococci (ranging from "1" to greater than "90"), including for example, Types 1, 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52, 55 and 56.

Paragraph beginning at page 2, line 19 has been amended as follows:

Within other aspects of the present invention, vaccinating agents are provided for promoting an immune response against Group A streptococci, comprising (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating a protective immune response against Group A streptococci, and (b) a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is not required to stimulate an immune response against Group A streptococci. As above, the polypeptide may be selected from a wide variety of Group A streptococci (ranging from "1" to greater than "90"), including for example, types 1.1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52, 55 and 56. Within certain further embodiments, the vaccinating agent may further comprise an

adjuvant, such as, for example, alum, Freund's adjuvant, and/or an immunomodulatory cofactor (*e.g.*, IL-4, IL-10, γ-IFN, or IL-2, IL-12 or IL-15).

Paragraph beginning at page 5, line 7, has been amended as follows:

As noted above, the present invention provides vaccinating agents suitable for preventing Group A streptococcal infections. Briefly, as described in more detail below it has been discovered that, in order to optimize the immunogenicity of all aspects of a multivalent vaccine. Within one aspect of the invention, immunogenic synthetic fusion polypeptides which stimulate an immune response against Group A streptococci are provided. Such polypeptides generally comprise (a) at least two immunogenic ~~polypetides~~ polypeptides from a Group A streptococci of at least 10 amino acids in length which are capable of stimulating an immune response against Group A streptococci, and (b) a peptide C terminal to the immunogenic polypeptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide is not required to stimulate an immune response against Group A streptococci. Particularly preferred protective peptides are generally at least ten amino acids in length, and may be 30 amino acids or longer.

Paragraph beginning at page 18, line 28, has been amended as follows:

Opsonic M protein antibodies 28correlate with protection against infection with the same serotype of group A streptococci (Lancefield, R.C., "Current knowledge of the type specific M antigens of group A streptococci," *J. Immunol. 89*:307-313, 1962; Lancefield, R.C., "Persistence of type-specific antibodies in man following infection with group A streptococci," *J. Exp. Med. 110*:271-282, 1959). Two related in vitro assays are used to detect opsonic antibodies in immune sera. The first is a screening assay that measures opsonization in mixtures of immune serum, whole, nonimmune human blood and the test organism (Beachey *et al.*, "Purification and properties of M protein extracted from group A streptococci with pepsin: Covalent structure of the amino terminal region of the type 24 M antigen," *J. Exp. Med. 145*:1469-1483, 1977). 0.1 ml of test serum is added to a standard number of bacteria and incubated for 15 minutes at room temperature. 0.4 ml of lightly heparinized human blood is added and the entire mixture is rotated end-over-end at ~~370~~ 37°C for 45 minutes. At the end of the rotation, smears are prepared on

microscope slides that are air-dried and stained with Wright's stain. "Percent opsonization" is quantitated by counting the percentage of polymorphonuclear leukocytes that have ingested or are associated with bacteria. An interpretable assay must have a preimmune control value that is 10% opsonization or less.

Paragraph beginning at page 19, line 17, has been amended as follows.

Confirmation of the presence of opsonic antibodies is obtained by indirect bactericidal antibody assays according to the original description by Lancefield (Lancefield, R.C., "Current knowledge of the type specific M antigens of group A streptococci," *J. Immunol. 89*:307-313, 1962). This assay is performed using test mixtures as described above except that fewer bacteria are added and the rotation is allowed to proceed for 3 hours. At the end of the rotation, pour plates are made in sheep blood agar and bacteria surviving are quantitated after overnight growth at ~~370~~ 37°C. Percent killing in the presence of immune serum is calculated by comparing to the growth in nonimmune serum.

Paragraph beginning at page 20, line 4, has been amended as follows:

Protective efficacy of M protein vaccines is determined by either indirect or direct (passive or active immunization) mouse protection tests. Indirect tests are performed by giving mice 1 ml of immune or preimmune serum via the intraperitoneal (i.p.) route 24 hours prior to challenge infections with the test organism given i.p. (Beachey *et al.*, "Human immune response to immunization with a structurally defined polypeptide fragment of streptococcal M protein," *J. Exp. Med. 150*:862-877, 1979). For each test organism, groups of 25 mice receive either preimmune ~~of~~ or immune serum. The animals are then divided into 5 groups of 5 mice each and 10-fold increasing challenge doses of virulent streptococci are given to each subgroup. After 7 days of observation, the ~~LD50~~ 50% lethal dose (LD_{50}) is calculated for each serotype tested.

Paragraph beginning at page 20, line 22, has been amended as follows:

In order to show directly the protective efficacy of opsonic antibodies evoked by the hexavalent vaccine, mice were immunized with the vaccine adsorbed to ALUM and then challenged with two of the serotypes represented in the vaccine. Female outbred white Swiss

mice were immunized via the ~~I.M.~~ i.m. route in the hind leg according to the following schedule: time 0, 25~~ug~~ µg; 3 weeks, 25 ~~ugug~~; 6 weeks, 50 ~~ug~~ µg; and 13 weeks, 50-~~ug~~ µg. Challenge experiments were performed on the 20 immunized mice and 20 control, unimmunized mice (~~Table 1.~~)). The challenge strains were types 24 and 19, with the reasoning that the M24 peptide is the largest fragment in the hexavalent protein and is reiterated and the M19 fragment is one of two that are only 35 amino acids long. These two fragments should reflect the range of protective immunogenicity of the hexavalent protein. ~~Interperitoneal~~ Intraperitoneal challenge of mice with virulent streptococci is the most stringent laboratory assay for opsonic antibodies.

Paragraph beginning at page 21, line 23, has been amended as follows:

To assure that none of the M protein vaccines evokes tissue-crossreactive antibodies, indirect immunofluorescence assays are performed using frozen sections of human heart, kidney, and brain (Dale, J.B. and Beachey E.H., "Protective antigenic determinant of streptococcal M protein shared with sarcolemmal membrane protein of human heart," *J. Exp. Med. 156*:1165-1176, 1982). Thin sections of tissue obtained at autopsy (4µm) are prepared on microscope slides and stored in a sealed box at ~~-700C~~ -70°C until use. Test serum is diluted 1:5 in PBS and dropped onto the tissue section. Control slides are made with preimmune serum and PBS. The slides are incubated at ambient temperature for 30 minutes and then washed three times in PBS in a slide holder. Fluorescein-labeled goat anti-IgG/IgM/IgA is diluted 1:40 in PBS and dropped onto the slides which are again washed, dried, and mounted with 1% Gelvetol and a coverslip. Fluorescence is detected using a Zeiss Axiophot microscope equipped with a xenon light source. Immunofluorescence is recorded using a scale of 0-4+, with 0 being no fluorescence and 4+ being that obtained with a standard, positive antiserum raised in rabbits against whole type 5 M protein (Dale, J.B. and Beachey, E.H., "Multiple heart-cross-reactive epitopes of streptococcal M proteins," *J. Exp. Med. 161*:113-122, 1985).

Paragraph beginning at page 22, line 20, has been amended as follows:

Three rabbits each were immunized with 100 ~~ug~~ µg doses of the hexavalent vaccine in either alum ~~of~~ or CFA. Booster injections of the same dose were given at 4 and 8 weeks in either alum or saline, respectively. ELISA titers were determined using the

purified hexavalent protein as the solid phase antigen (Figure 3). Sera from the animals that received the hexavalent vaccine in alum had antibody titers that were equal to or greater than the sera from rabbits that received the same dose in CFA. In a subsequent experiment, three rabbits were ~~immunized I.M.~~ i.m. with 100 ~~ug~~ µg of the hexavalent vaccine in saline alone according to the same schedule. None of these rabbits developed significant antibody titers against either the immunogen or the respective pep M proteins (data not shown). These data indicate that alum is a suitable and necessary adjuvant for the multivalent vaccine and is equal to the adjuvant activity of CFA in combination with the hexavalent protein.

In the Claims:

Claims 13, 14, 18, 20, 22, 24-26, 28, 29, 33, 35, 39, 41, 43 and 45-48 have been canceled without prejudice as set forth above.

All currently pending claims have been included for the Examiner's convenience. Claims 12, 15-17, 19, 21, 23, 27, 30, 32, 36-38, 40, 42, and 44 have been amended and new claims 54-58 have been added, as follows:

12. (Amended) A recombinant fusion polypeptide, comprising:

(a) ~~an~~ a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(b) a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide ~~is in addition to the immunogenic portion~~ is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion and is not required to stimulate an immune response against Group A Streptococci.

15. (Amended) The polypeptide according to ~~any one of claims 12-14~~ claim 12 wherein at least one of the immunogenic peptides is from a Group A Streptococci

serotype selected from the group consisting of 1, ~~1.1,~~ 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 and 56.

16. (Amended) The polypeptide according to claim ~~15~~ 12 wherein the immunogenic portion ~~comprises~~ consists of six immunogenic peptides, wherein the peptides are an amino-terminal portion of at least one M protein.

17. (Amended) The polypeptide according to any one of claims ~~12-14~~ 12 or 15-16 wherein at least one of the immunogenic peptides is from a serotype ~~1~~ 11 Group A Streptococci.

19. (Amended) The polypeptide according to any one of claims ~~12-14~~ 12 or 15-16 wherein at least one of the immunogenic peptides is from a serotype ~~4~~ 13 Group A Streptococci.

21. (Amended) The polypeptide according to any one of claims ~~12-14~~ 12 or 15-16 wherein at least one of the immunogenic peptides is from a serotype ~~5~~ 22 Group A Streptococci.

23. (Amended) The polypeptide according to any one of claims ~~12-14~~ 12 or 15-16 wherein at least one of the immunogenic peptides is from a serotype ~~6~~ 28 Group A Streptococci.

27. (Amended) A composition for promoting an immune response against Group A Streptococci, comprising:

(a) a recombinant fusion polypeptide, comprising:

(i) ~~an~~ a multivalent immunogenic portion wherein the immunogenic portion comprises at least two immunogenic peptides, the peptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(ii) a C-terminal peptide which protects the immunogenicity of the immunogenic portion, wherein the C-terminal peptide ~~is in addition to the immunogenic portion~~ is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion ~~and is not required to stimulate an immune response~~ against Group A Streptococci; and

(b) a pharmaceutically acceptable excipient or diluent.

30. (Amended) The composition according to ~~any one of claims 27-29~~claim 27, further comprising an adjuvant.

31. The composition according to claim 30 wherein the adjuvant is alum or Freund's adjuvant.

32. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31, further comprising an immunomodulatory cofactor.

34. The composition according to claim 32 wherein the immunomodulatory cofactor is selected from the group consisting of IL-4, IL-10, γ-IFN, IL-2, IL-12, and IL-15.

36. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31 wherein at least one of the immunogenic peptides is from a Group A Streptococci serotype selected from the group consisting of 1, ~~1.1,~~ 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 and 56.

37. (Amended) The composition according to ~~claim 35~~ any one of claims 27 or 30-31 wherein the immunogenic portion ~~comprises~~ consists of six immunogenic peptides, wherein the peptides are an amino-terminal portion of at least one M protein.

38. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31 wherein at least one of the immunogenic peptides is from a serotype ~~1~~–11 Group A Streptococci.

40. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31 wherein at least one of the immunogenic peptides is from a serotype ~~4~~–13 Group A Streptococci.

42. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31 wherein at least one of the immunogenic peptides is from a serotype ~~5~~–22 Group A Streptococci.

44. (Amended) The composition according to any one of claims ~~27-29~~27 or 30-31 wherein at least one of the immunogenic peptides is from a serotype ~~6~~–28 Group A Streptococci.

54. (New) The polypeptide according to any one of claims 12 or 27 wherein only one immunogenic peptide is reiterated.

55. (New) The polypeptide according to claim 16 wherein each M protein portion is from a different Group A Streptococcal serotype, the serotypes being 1, 3, 5, 6, 19, and 24.

56. (New) The polypeptide according to any one of claims 12 or 27 wherein the immunogenic portion consists of ten immunogenic peptides, wherein the peptides are an amino-terminal portion of a M protein.

57. (New) The polypeptide according to claim 56 wherein each M protein portion is from a different Group A Streptococcal serotype, the serotypes being 1, 3, 5, 6, 18, 19, 22, 24, 28, and 30.

58. (New) The polypeptide according to any one of claims 12 or 27 wherein the immune response against Group A Streptococci comprises opsonic antibodies that do not cross-react with human tissue.

induction of